

Potential of Mean Force Calculation of Solute Molecules in Water by a Modified Solvent-Accessible Surface Method

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ABSTRACT: We propose an empirical method for evaluating the potential of mean force (pmf) of solute molecules in water by modifying the solvent-accessible surface (SAS) method described by Eisenberg et al. We re-evaluated the SAS energy for each united atom composing the solute. We took into account the energy required to generate a void between adjacent solute molecules and the Coulombic interactions between atom-centered point charges of solute molecules containing C, O, P, K⁺, Na⁺, and Cl⁻ atoms in water. The modified SAS method well reproduced the various pmfs given by MD calculations or the integral equation method. The large activation energy of K⁺-18-crown-6 complexation can be explained mostly by the void energy. The computational time required for the modified SAS method is approximately three to four orders of magnitude less than that by MD calculations. © 1997 John Wiley & Sons, Inc. *J Comput Chem* **18**: 1656–1663, 1997

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Introduction

The calculation of potential of mean force (pmf) is well established theoretically,^{1,2} such as in the free energy perturbation method, the thermo-

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dynamic integration method based on molecular dynamics (MD) simulation, the integral equation (IE) method, and so on. The IE method provides pmfs in a much shorter cpu time than MD. Pettit et al. calculated the ϕ - ψ plot of *N*-acetyl-alanyl-amide in water by the IE method.³ However, the calculations are still not fast enough to study large biomolecules like proteins because hundreds or thousands of energy calculations must be made for a protein-protein binding problem and a long simulation time is required for protein dynamics.

On the other hand, the solvent-accessible surface (SAS) area seems to be a good measure for evaluating the solvation energy, as shown by Eisenberg et al.,⁴ Ooi et al.,⁵ Friedman et al.,⁶ and Still et al.⁷ These methods are based on the assumption that the solvation free energy change is proportional to the SAS area, $\Delta G = \sum \sigma_i A_i$, where the atomic solvation parameters, σ_i , are obtained empirically. This simple method is actually very useful. Some trials were made for simulating protein folding.^{8,9} Rapid algorithms for computing SAS area have been developed recently.^{10–12} These methods seem applicable to estimate the pmf for solute–solute interaction in solvent. However, many of the pmfs by MD calculations or the IE method are not so simple (e.g., having a double minimum shape as discussed later) to simulate by the SAS methods previously mentioned. Therefore, we tried to construct a new empirical method. We paid attention to the generation/annihilation energy of the void that can occur between two adjacent solute molecules in solvent. The distance between the two minima in the pmfs is usually close to the diameter of the solvent molecule.

Scaled particle theory (SPT)^{13–16} is able to give the free energy change of formation of a spherical cavity and the solvation free energy. This theory has been applied on a nonspherical cavity of molecule.¹⁷ Recently, Hummer et al. gave a clear explanation of the information theory method for computing the formation energy of a cavity of general shape.¹⁸ The original SPT gives the energy in an analytical form that is a polynomial of the radius of the sphere describing the cavity. However, SPT cannot be applied directly to the pmf calculations, because the energy calculated by SPT includes the so-called “point insertion energy,” which depends on the number of solute particles. When two solute molecules approach and contact, we cannot recognize when the two solute molecules become one cluster. The information theory model gives the energy in a numerical form, which includes a volume integral on six dimensions. This theory was applied to the hydrophobic interaction and successfully reproduced the double minimum shape of the methane–methane pmf.¹⁸ However, the six-dimensional integral of the information theory model seems too difficult to apply to a protein.

Rashin calculated the ion–ion pmf based on the Poisson–Boltzmann electrostatic energy calculation¹⁹ using a continuum model, and suggested the importance of the void region in which two solutes exist and the solvent water cannot pene-

trate. His result showed that the double minimum curve of pmf of the positive–negative ion pair is due to the energy of unscreened Coulombic interaction in the void. However, this method could not explain the similar double minimum shape of pmfs for negative-ion pairs (e.g., Cl^- – Cl^- or F^- – F^-) as reported recently,^{20,21} and, obviously, would be time consuming to calculate large biomolecules.^{22–26}

The calculation of the solvation free energy based on the combination of the SAS method and the Poisson–Boltzmann equation has been reported by many investigators,^{27–38} but the shapes of the pmfs were not calculated or not well examined in comparison with the pmfs by MD. Previously, we presented the modified SAS method and used it to calculate pmfs for methane and water.³⁹ When two solute molecules (or atoms) approach each other sufficiently closely, a void too small for water molecules to penetrate is generated between the two solutes. By taking into account the energy contribution from this void, we have been able to reproduce the double minimum shape of the pmfs of the methane and octane pairs in water as shown by MD calculations.³⁹

In this study, we reconstructed the atomic solvation parameters for atoms that biomolecules are mainly composed of, considering the void energy and simple screened Coulombic interactions.

Method

We assume that the interaction energy of solutes in solvent consists of four terms: van der Waals (vdW) repulsion (E_{vdW}); the contribution from the SAS (E_{SAS}); the contribution from the void volume (E_{void}); and the contribution from the Coulombic interaction (E_{c}).

$$E_{\text{total}} = E_{\text{c}} + E_{\text{SAS}} + E_{\text{void}} + E_{\text{vdW}} \quad (1)$$

where

$$E_{\text{c}} = 332 \sum_{i < j} \frac{q_i q_j \exp(-\kappa r)}{\epsilon r} \quad (2)$$

where q_i and q_j are the atomic point charges of atoms i and j in atomic units, ϵ is the dielectric constant of the solvent, and κ is the Debye–Hückel parameter. The units of energy, charge, and distance are kilocalories per mole, positron charge, and angstroms (Å), respectively.

By definition, E_{SAS} is the sum of the SAS energy of each atom, which forms the solute molecule;

$$E_{\text{SAS}} = \sum_i \sigma_i * A_i \quad (3)$$

where A_i is the SAS area of each atom measured in \AA^2 and σ_i is the atomic solvation parameter in $\text{kcal}/(\text{\AA}^2 \text{ mol})$. In the present case, the atomic solvation parameters must be empirically reconstructed accounting for the Coulombic interaction and the void energy separately.

Forming an infinitesimal void at a fixed position in a solvent causes a free energy change, $\Delta F = -kT \log p$, where p is the probability of a point insertion, which the solvent molecules cannot go through in their thermal motion, as described by SPT.¹⁶ As two solute molecules (or atoms) approach, the water molecules between the solutes must be excluded and a void will be generated. This void formation first causes an entropy reduction and then an increase in free energy of the system for the same reason as described before. Because the region between two solutes is anisotropic, the analysis and the estimation of this effect are not easy. In extended scaled particle theory, the cavity formation energy is given by the excluded volume and its derivatives,¹⁷ and it does not explicitly depend on the shape of the surface. Therefore, we simply assume that this effect (E_{void}) can be described by:

$$E_{\text{void}} = \theta * v \quad (4)$$

where θ is a proportionality coefficient and v is the void volume in \AA^3 . For water, we assume that θ is $0.3 \text{ kcal}/(\text{\AA}^3 \text{ mol})$ and is independent of the void shape. This value was found by fitting eqs. (1)–(5) on the methane–methane and octane–octane pmfs by MD calculations.³⁹

We calculate the void volume around the solutes within the solvent-accessible surface. Figure 1 shows our method of approximating the void volume. The water molecule is approximated by a sphere with a radius of 1.4 \AA . We consider the shell between the van der Waals (vdW) surface of the solute and its solvent-accessible surface, which is 1.4 \AA outside surface of the vdW surface. We divide this shell into two concentric shells: the outer shell and the inner shell, the latter shown as the shaded region in Figure 1. Because a spherical solvent molecule contacts with a solute sphere at a point on the vdW surface, the inner shell is always void-rich. We use the void volume indicated with an arrow as the effective void volume for the pmf

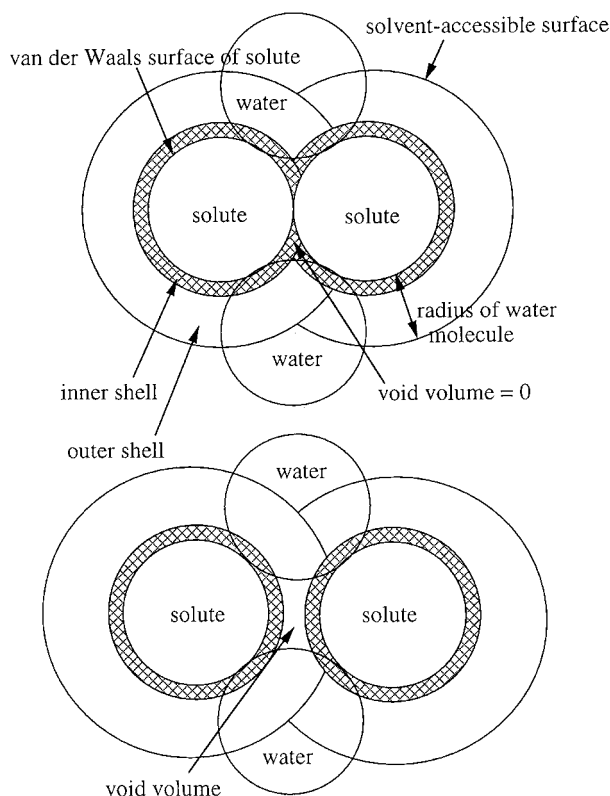


FIGURE 1. Schematic representation of the void volume in a solution. The shaded rings and the empty rings represent the inner and outer shells, respectively. The interstitial volume surrounded by the two adjacent solutes and adjacent water molecules is the void, and the empty part of the void is the effective void.

calculations. When two solutes are in contact, the effective void volume must be zero. Taking this into account, we find that the thickness of the inner shell is 0.3 \AA for the alkane in water system. This is a rough approximation of the void volume. This void generation effect gives a hump on the pmf curve like the one made from the unscreened Coulombic interaction.¹⁹ The former is a totally entropic effect, and the latter is a totally enthalpic effect.

The E_{vdW} was approximated as the sum of exponential type potential functions:

$$E_{\text{vdW}} = c_1 * \sum_{i < j} \exp(-c_2 * (r_{ij} - (\rho_i + \rho_j))) \quad (5)$$

where c_1 and c_2 are determined by fitting eq. (5) to the pmf of a methane pair in vacuum obtained by MD simulations. We determined that $c_1 = 0.2$ and $c_2 = 5$. The ρ_i and ρ_j stand for the vdW radii of atoms i and j , respectively. Eq. (5) was used to

realize a "rounded" hard-sphere model to stabilize the computation. We omit the attractive force term in the vdW potential between solutes in water to avoid complicating our method. In the present empirical method, the vdW and Coulombic forces between a water molecule and a solute are included in the SAS energy. Figure 2 shows schematically the expected pmf by the modified SAS method, where the pmf curve shows a distance oscillation having a deep minimum, a hump, and a shallow minimum. The hump is obviously due to the void energy. Then σ_i of E_{SAS} is the only adjustable parameter to fit the deep minimum to that of the pmf by MD simulation.

Parameter Determination and Results

The atomic parameters in eqs. (2)–(5) were determined using the following fitting procedure to the results/data previously obtained: the pmf³⁹ of a methane pair in water for the alkyl-carbon atoms; the pmfs⁴⁰ of a benzene pair in water for the aromatic carbon atoms; the pmfs⁴¹ of $\text{Na}^+\text{--Cl}^-$ in water for Na^+ and Cl^- ; the pmfs⁴² of a water pair and a water–methane pair in water for oxygen; the pmf⁴³ of a $\text{PO}_4\text{Me}_2^-\text{--Na}^+$ pair for phosphorus; and the pmf⁴⁴ of a $\text{K}^+\text{--}18\text{-crown-6}$ pair for K^+ . In this procedure, we set the dielectric constant of the solvent to 50 in eq. (2) referring to previous re-

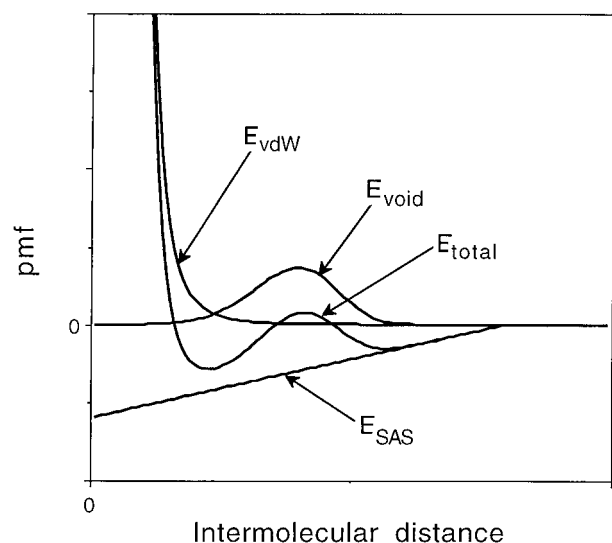


FIGURE 2. Schematic image of pmf curve given by the modified SAS method. $E_{\text{total}} = E_c + E_{\text{SAS}} + E_{\text{void}} + E_{\text{vdW}}$, where: E_c = Coulombic interaction; E_{SAS} = SAS energy; E_{void} = void energy; and E_{vdW} = van der Waals repulsion given by eqs. (2)–(5).

ports^{45–47} because we analyze the intermolecular forces acting within 10 Å. It should be noted that the accuracy levels of the pmfs obtained by MD or IE methods sometimes seem low, especially when the system includes charged or polar solutes. Several pmfs of methane–methane have been reported so far.^{39,48–51} Usually, the simple point charge (SPC) model or the transferable intermolecular potential (TIP) water model without electronic polarization were used in these studies. Van Belle et al. calculated the pmf with the electronically polarizable water (PSPC) model⁴⁸ and found that the correlation functions of the methane–water and water–water do not change from those of the SPC–water model, and the double minimum shape of the pmf of methane–methane is obvious.

Thus, the basic line shapes of those pmfs are similar, having a deep minimum, a hump, and a shallow minimum. We examine the modified SAS method in regard to the positions and the levels of the minima and the maxima. Figure 3a–d shows the pmfs of solute pairs in water calculated by the modified SAS method and those previously calculated using MD or the IE method for the following cases. It should be noted that most MD calculations are based on the all-atom model, whereas our modified SAS method used the united-atom model; that is, a united O atom for the OH group and a united N atom for NH_4^+ . Therefore, the pmf curves given by our method may shift to the right, as compared with the all-atom model, by the size (up to 0.3 Å) of covalently bonded hydrogen atoms. In the united-atom model, a water molecule is approximated with a sphere by averaging over their rotational motion, so the atomic radius is not necessarily equal to the usual vdW radius.

(a) Comparison of the pmfs of methane–methane (C–C),³⁹ methane–water (C–O), and water–water (O–O) pairs⁴² in water by MD and those by the present SAS method. The modified SAS method reproduced the model pmf curves of C–C well, but those for C–O and O–O roughly. Setting the water radius as a constant value (1.4 Å) seems to cause some discrepancies in C–O and O–O pmfs. We might have to treat O's in C–O and O–O with different atom parameters. In these calculations, the thickness of the inner shell was 0.3 Å (see ref. 39). According to Belle and Wodak,⁴⁸ the peak of the radial distribution function was found not at 3.4 (= 2.0 + 1.4) Å but 3.7 Å for water around a methane. In addition, the small peak at 3.5 Å for the O–O pmf by MD is due to the hydrogen bond property (tetrahedral structure) of

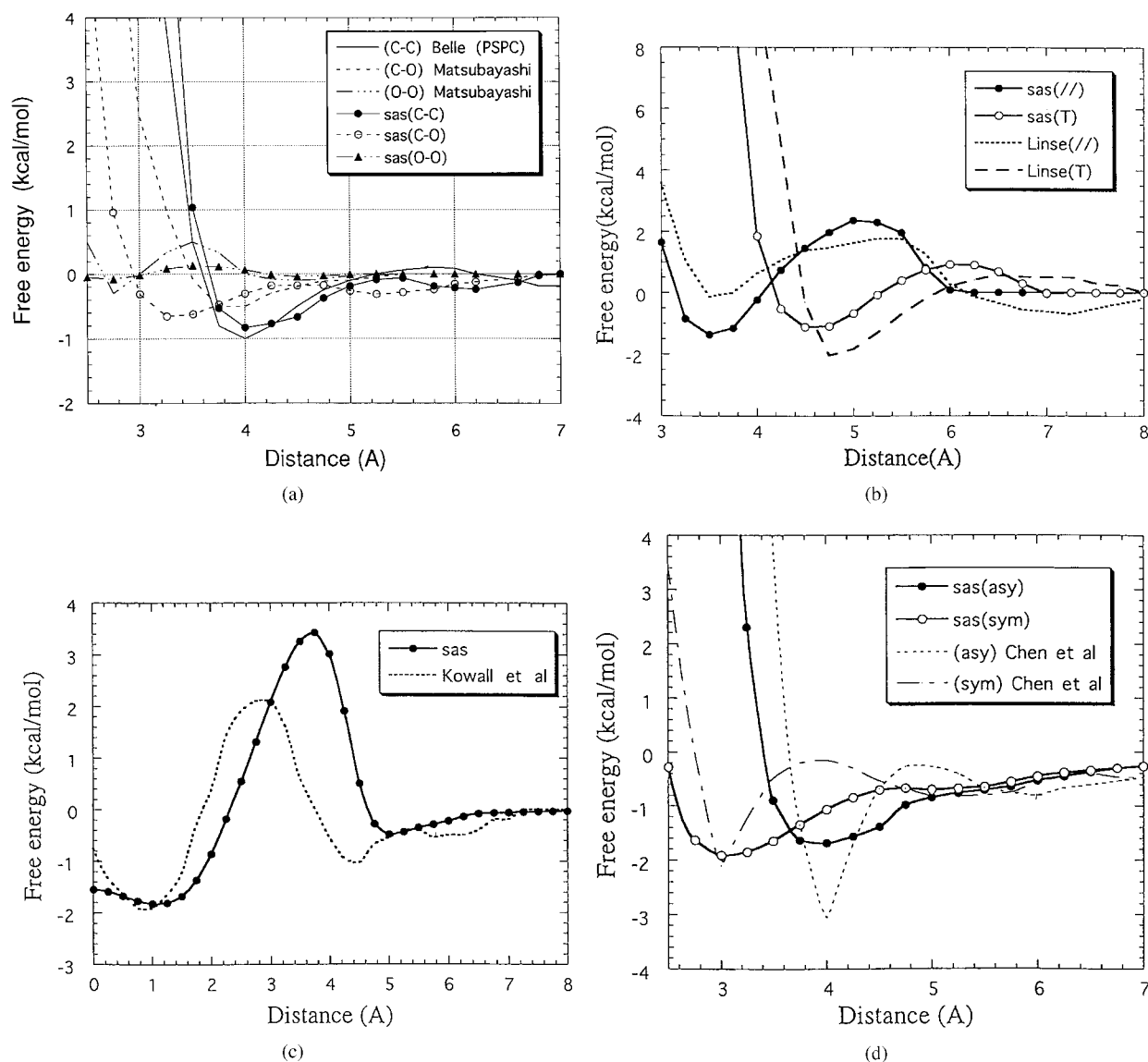


FIGURE 3. Comparison of the pmf of solute pairs in water by MD and by the empirical method. The “SAS” label means the pmf calculated by the modified SAS method. (a) Comparison of the pmf of methane–methane,³⁹ methane–water, and water–water pairs⁴² in water by MD and the empirical method. The distance is measured between the atoms indicated. (b) Benzene pair.⁴⁰ The “//” sign indicates a parallel approach of the benzene pair, and “+” indicates a perpendicular approach. The distance is measured between the ring centroids. (c) K⁺–18-crown-6 pair.⁴⁴ The distance is measured between the K⁺ center and the crown centroid. (d) Na⁺–PO₄Me₂⁻ pair.⁴³ The distance is measured between the Na⁺ center and the P center.

water. Such a fine structure cannot be simulated by this simple empirical method and is not our present target.

(b) *Benzene pair*.⁴⁰ The intermolecular distance means the distance between the centers of two benzenes. We used two different approaches. The first approach is a “parallel approach” (//) in which two benzene molecules were kept parallel. The second is a “T-shape approach” (+) in which

they are kept perpendicular to each other. There is a fair agreement between the SAS and MD pmf curves. The inner shell thickness of 0.4 Å was used. The main discrepancy between them is due to the size of hydrogen atoms of benzene and water. The MD calculation was done with the all-atom model, whereas our method used the united-atom model. The potential functions of the 1984 MD simulations were based on *ab initio*

Hartree–Fock calculations which showed that the T-shape is more stable than the parallel conformation,⁵² and the interaction energy of benzene dimer was -2 kcal/mol for the parallel conformer and -3.5 kcal/mol for the T-shape conformer. In contrast, a recent high-level *ab initio* Hartree–Fock Møller–Plesset calculation showed that the parallel alignment (slightly slid) was the most stable, and the T-shape is not at a minimum but rather a saddle point, and the interaction energy was -2.13 kcal/mol for the parallel alignment, -3.33 kcal/mol for the parallel (slightly slid) alignment, and -2.84 kcal/mol for the T-shape alignment.⁵³ These results suggest that the force field of benzene may need to be developed further. Thus, although the pmfs by MD have not yet been converged completely, they have similar profiles to one another. Our modified SAS method basically agrees well with MD results, except for fine structure.

(c) K^+ –18-crown-6 pair.⁴⁴ We set $\kappa = 1/16 \text{ \AA}^{-1}$, which corresponds to a KCl concentration of 20 mM. We adopted Cl^- as the counteranion. The center of the crown, the cation, and the anion were located along a straight line in the order crown– K^+ – Cl^- . The distance between the crown and the cation and the distance between the cation and the anion were optimized by minimizing the energy calculated by the modified SAS method. The cation approaches the crown ether along the axis perpendicular to the plane made by the six oxygen atoms of the crown ether. The intermolecular distance stands for the distance from the cation to the center of the crown ether.

The present SAS method reproduced a large hump at 3.5 \AA corresponding to the activation energies of complexation (4.0 kcal/mol) and dissociation (5.3 kcal/mol) and the stabilization energy

(-1.8 kcal/mol). These activation energies are caused by the energy to generate a void between two solutes. These values are a little larger than that of MD, but smaller than the experimental values of complexation (6.4 kcal/mol) and dissociation (9.3 kcal/mol) and the stabilization energy (-2.9 kcal/mol).⁵⁴ According to Rashin,¹⁹ the unscreened Coulombic interaction in the void occupied by two solutes gives a hump in the pmf curve at a similar or a slightly more separated position than that by the intersolute void which we are evaluating. If a more precise estimation of Coulombic interactions could be adopted, our results may improve. The complexation energy of the crown– K^+ complex was reported to be 18 kcal/mol in 1989,⁵⁵ 7 kcal/mol in 1990,⁵⁶ and 2.9 kcal/mol in 1995.⁴⁴ Furthermore, the two older calculations showed no activation energy for complexation. Thus, our result is the first physical explanation of the activation energy of K^+ –18-crown-6 complexation.

(d) Na^+ – $\text{PO}_4\text{Me}^{2-}$ pair.⁴³ “Symmetric” means Na^+ approaching the P atom along the axis of the bisector of the OPO angles in the PO_2 plane, whereas “asymmetric” means Na^+ moving along the O–P bond vector. The atom-centered point charges were determined by Chen et al.⁴³ We set $\kappa = 1/16 \text{ \AA}^{-1}$. In the symmetric approach, Na^+ can access the P atom at only 5% of the total of vdW surface, and in the asymmetric approach it is totally inaccessible so that the estimated σ of P should have an error larger than those of the other atoms. Nevertheless, our method reproduced the positions of the minima shown by MD. Generally, if the system includes polar or ionic solutes, the hump height will be underestimated by our method, as indicated by Rashin.¹⁹

TABLE I.
Parameters for Modified SAS Method.^a

Atom	Atom type	ρ (\AA)	σ ($\text{cal} / \text{\AA}^2 / \text{mol}$)	Charge	Notes
C	C1	2.0	25	+/-	Alkyl, Figure 3A
C	C2	1.7	20	+/-	Aromatic, Figure 3b
C	C3	1.55	20	+/-	C=O
O	O1	1.2	5	0	Water, Figure 3A
O^-	O2	1.4	15	–	–OH, =O, ester, Figure 3c
Cl^-	C1	1.8	15	–	Fitted to Ref. 41
Na^+	Na	1.0	10	+	Fitted to Ref. 41
K^+	K	1.3	10	+	Figure 3c
P^+	P	1.9	10	+	Figure 3d

^a The “C” and “O” include the attached hydrogen atoms: CH_n ($n = 4 \sim 2$) and OH_n ($n = 2$). Each atom is assumed to be spherical.

TABLE II. **Stabilization Energy (Kilocalories per Mole) of Crown Ether and Cation Complexes in Water by Modified SAS Method Compared with Experimental Data.**⁵⁷

	Na ⁺	K ⁺
⟨18-crown-6⟩		
Experimental	0.96	1.00
Calculation	0.58	1.26
⟨15-crown-5⟩		
Experimental	1.15	2.81
Calculation	1.30	1.59

The parameters for each atom are summarized in Table I. The values of stabilization energy obtained by the modified SAS method between a crown ether (15-crown-5 or 18-crown-6) and a cation (Na⁺ or K⁺) in the presence of a counteranion at 298 K in water are compared with the experimental data⁵⁷ in Table II, where we see good agreement.

Hydrogen Bonding

Eisenberg et al.⁴ determined the atomic solvation parameters for oxygen to be $-6 \sim -24$ cal/(Å² mol) and for nitrogen to be -50 cal/(Å² mol), whereas Ooi et al.⁵ determined values for O and N to be -172 cal/(Å² mol) and -132 cal/(Å² mol), respectively. The methods in Refs. 4 and 5 do not include a Coulombic potential explicitly. Because a negative atomic solvation parameter indicates a repulsive interaction, these parameters are inadequate for representing hydrogen bonding in peptides ($-\text{NH} \cdots \text{O} = \text{C} <$). Our method, which includes a simple Coulombic interaction, provides positive solvation parameters for O and N to be $+5$ cal/(Å² mol) and $+10 \sim 20$ cal/(Å² mol), respectively, and can represent the hydrogen bond affinity. Here, the atomic solvation parameter for nitrogen was roughly determined according to the stabilization energy of NH₄⁺-18-crown-5 obtained experimentally.⁵⁷

There have been many discussions about the radius of an ion in solvent. The ion radius in solvent is different from the radius in crystal, and depends on the solvent structure.⁵⁸ Scheraga⁵⁹ and Hagler et al.⁶⁰ reported different values of the radius of the $>\text{NH}$ group (1.55 and 1.825 Å), a respectively, whereas the optimized potentials for the liquid simulation (OPLS) parameter⁶¹ for the $-\text{NH}_3^+$ group radius is 1.965 Å. The radius of the

NH₄⁺ ion should be close to the radius of the $-\text{NH}_3^+$ group. When adopting 1.9 Å as the radius of NH₄⁺ and 10 cal/(Å² mol) as the solvation parameter in the modified SAS method, the calculated stabilization energy values of NH₄⁺-18-crown-6 and NH₄⁺-15-crown-5 become 1.32 and -0.57 kcal/mol, respectively, which agree in signs and rough magnitudes with the experimental values of 1.68 kcal/mol and -1.83 kcal/mol, respectively⁵⁷ (see Table II).

Thus, because the modified SAS method provides the positive solvation parameters by taking into account simple screened Coulombic interactions, the affinity of hydrogen bonding is roughly represented by our method except for the bond direction. To represent anisotropic hydrogen bond, the H atom must be calculated explicitly. Our treatment of the Coulombic interaction is too simple to represent the repulsion due to the unscreened Coulombic interaction as Rashin showed. As a result, our method may underestimate the hump height between two minima of the pmfs of ionic or polar solutes down to the almost half of its magnitude.

The original SAS method sometimes seems to fail as mentioned in a report on cyclic hydrocarbon compounds.⁶² If we adopt different solvation parameters for methyl and methylene groups, the SAS method will still be effective. This is a problem to be examined in the future.

Conclusion

The modified SAS method for evaluating the potential of mean force of solute molecules in water was empirically reconstructed. In addition to the SAS energy, the energy required to generate a void volume between adjacent solute molecules and the energy contribution due to Coulombic interactions were taken into account. Based on the pmfs of solute molecules in water obtained to date by molecular dynamics simulations, we determined the parameters necessary to calculate the pmfs for solute molecules containing C, O, P, K⁺, Na⁺, Cl⁻, and N. It should be noted that we did not adopt the Poisson-Boltzmann method to calculate the Born energy so that the accuracy of E_c may not be sufficient to reproduce the pmfs of charged solutes closely. However, in general, the present modified SAS method successfully reproduced the pmfs of various solute molecules in water by MD simulations and integral equation methods.

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